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Enantioselective Total Synthesis of Brevetoxin A: Convergent Coupling Strategy and Completion

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Abstract

A highly convergent, enantioselective total synthesis of brevetoxin A is reported. The development of a [X + 2 + X] Horner–Wadsworth–Emmons/cyclodehydration/reductive etherification convergent coupling strategy allowed for a unified approach to the synthesis of two advanced tetracyclic fragments from four cyclic ether subunits. The Horner–Wittig coupling of the two tetracyclic fragments provided substrates that were explored for reductive etherification, the success of which delivered a late-stage tetraol intermediate. The tetraol was converted to the natural product through an expeditious selective oxidative process, followed by methylenation.

Keywords

asymmetric synthesis; convergent strategy; ladder toxin; polycyclic ether; total synthesis

Introduction

In the preceding manuscript,[1] we described the development of efficient routes to the B, E, G, and J ring subunits **7**-**10** of brevetoxin A (**1**) (Scheme 1), which provided multi-gram quantities of these key intermediates. Described herein is the convergent coupling of these subunits through a unified strategy to produce two advanced tetracyclic fragments **5** and **6**, the conversion of the tetracyclic fragments into Horner–Wittig coupling partners **3** and **4**, and the completion of brevetoxin A (**1**) via the late-stage nonacycle **2**.

Results and Discussion

Convergent Coupling Strategy for the Synthesis of the BCDE and GHIJ Fragments

In the context of the rapidly growing collection of synthetic strategies for the assembly of *trans/syn/trans*-fused polycyclic ether arrays,[2] we were attracted to the maximized convergency of the [X+2+X] concept[2b] in which two individual rings are coupled, followed by formation of two new, adjoining rings. Furthermore, based upon our overarching retrosynthetic analysis of brevetoxin A (Scheme 1), we recognized that a strategy of this type would be particularly well-suited for the convergent assembly of the individual BCDE and GHIJ subunits. Therefore, we designed a unique convergent coupling strategy that relies upon a Horner– Wadsworth–Emmons (HWE) reaction for the union of a cyclic ether functionalized

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as the β-keto phosphonate with another as the aldehyde (Scheme 2). The resulting enone intermediate would be subjected to 1,4-reduction, and an *endo*-selective cyclodehydration would provide a cyclic enol ether. Stereoselective hydration of the enol ether followed by a reductive etherification sequence would complete the tetracyclic subunit.

The HWE/cyclodehydration/reductive etherification strategy has several pertinent advantages. The mildness and reliable efficiency of the HWE reaction is particularly important for the stoichiometric coupling of advanced fragments—a critical consideration in the choice of assembly strategy. Also, the numerous methods for effecting 1,4-reduction of enones[3] and cyclodehydrations of δ-hydroxy ketones[4] bolster the potential for success of the strategy. Finally, the hydration and reductive etherification of enol ethers is well-known as one of the most powerful approaches for the closure of interior rings in a polycyclic ether array.[2] Strategically, for the BCDE tetracycle **5**, the B ring aldehyde **7** would be coupled with the E ring keto phosphonate **11**, which would derive from the E ring precursor **8**[1] (Figure 1).

Preparation of the suitably functionalized E ring keto phosphonate **11** was accomplished by converting primary alcohol **8** to the iodide **12**, which was displaced by cyanide to afford the nitrile **13** (Scheme 3). Partial reduction of the nitrile to the aldehyde was followed by an aldol reaction with the lithium carbanion of dimethyl methylphosphonate to produce β–hydroxy phosphonates **14** as an inconsequential mixture of diastereomers. Subsequent oxidation to the keto phosphonate[5] and ring-closing metathesis provided the E ring **11** in excellent yield.

For the Horner–Wadsworth–Emmons coupling of B ring **7** and E ring **11**, exposure of the two fragments to aqueous $Ba(OH)_2$ provided a 96% yield of the desired enone **15** (Scheme 3).[6] A method was next developed to directly access the enol ether **16** from enone **15.** Using Wilkinson's catalyst and Me_2PhSiH, the enone was reduced,[7] and subsequent addition of PPTS to the reaction mixture provided enol ether **16** in a one pot transformation. Since the presence of the E-ring endocyclic olefin precluded a straightforward Epoxidation of the electron rich enol ether **16** and in situ reduction of the sensitive epoxide proved particularly challenging. While dimethyldioxirane (DMDO) smoothly converted the enol ether to the corresponding epoxide, the epoxide proved to be extremely unstable. Various conditions were explored, but only use of “acetone free” DMDO to execute the epoxidation, followed by immediate exposure of the epoxide to $i Bu_2AlH$ at low temperature proved workable,[8] providing a mixture of diastereomeric secondary alcohols. Oxidation[9] of the alcohols produced a 3:1 mixture of ketones **17:18**, revealing that the epoxidation and in situ reduction had provided a 3:1 dr at C12, favoring the undesired configuration. This result was certainly not unexpected based on the influence of the C8 angular methyl on the approach of electrophiles to the C11–C12 enol ether double bond of **16.** Additionally, because of the 1,3-relationship of the C8 angular methyl and the C12 substituent, it was anticipated that major isomer **17** might be readily epimerized to **18**. After investigating several bases and solvent systems, it was discovered that subjecting the mixture of ketones to potassium carbonate in refluxing methanol provided a 3:1 dr at C12, favoring the desired configuration **18**.[10] Furthermore, the minor isomer could then be recovered and exposed to the same equilibration conditions, ultimately providing an excellent yield of the desired ketone **18**. Treatment of ketone **18** with camphorsulfonic acid in refluxing methanol provided the desired mixed methyl ketal **19** with loss of the primary TIPS protecting group,[11] and reductive etherification delivered the targeted BCDE tetracycle **5**.[12]

Based upon the effectiveness of our approach to the BCDE ring system, our vision for the GHIJ fragment **20** synthesis involved analogous coupling of a G ring keto phosphonate with a J ring aldehyde (Figure 2). We recognized that the choice of protecting groups employed in the GHIJ fragment synthesis would not only factor into the overall efficiency of the total synthesis, but could also prove critical in the success of key reactions. With preliminary experiments

revealing that silyl protecting groups were unsuitable for the J ring (i.e., $R^1 = SiR_3$, Figure 2) due to their lability under acidic conditions used in the synthesis, two strategies were conceived. While compelled by the robustness of the protecting groups in the coupling of G ring **21a** (R^2 = Piv, R^3 = TIPS) and J ring **22a** (R^1 = Bn), we were also attracted to the expedient coupling of G ring **21b** (R^2 = Bn, R^3 = PMB) and J ring **22b** (R^1 = Bz) in which protecting group manipulations from G ring intermediate **9** would be minimized. In either case, HWE coupling would lead to an enone intermediate, and subsequent 1,4-reduction and cyclodehydration would lead to an enol ether, poised for hydration and ultimate reductive etherification to produce the desired tetracyclic fragment **20a** or **20b**. In the end, both protecting group strategies were explored as viable routes toward the completion of the total synthesis.

The G ring intermediate **9** (Scheme 4) was first converted to keto phosphonate **21a** through an eight step sequence. After obtaining bis-TIPS ether **23** through a series of protecting group manipulations, selective removal of the primary TIPS group under acidic conditions followed by a two-step oxidation process[13] provided carboxylic acid **24** in excellent yield. Exposure to K_2CO_3 and MeI afforded the methyl ester, which underwent a Claisen condensation with lithiated dimethyl methylphosphonate to furnish the desired keto phosphonate **21a**. Alternatively, protection of G ring intermediate **9** as the bis-PMB ether, rapid removal of the TIPS group with H_2SiF_6,[14] and oxidation of the resultant alcohol with catalytic TEMPO revealed aldehyde **25** in 87% yield over three steps.[15] In this case, direct reaction of the aldehyde with lithiated dimethyl methylphosphonate was high yielding, and oxidation of the resultant β–hydroxy phosphonates **26** (inconsequential mixture of diastereomers) under Dess–Martin conditions afforded keto phosphonate **21b.** While keto phosphonate **21a** required three more steps from intermediate **9** than keto phosphonate **21b**, the overall yield was quite similar in both cases.

The J ring alcohol **10** was used to quickly access aldehydes **22a** and **22b** through three step sequences (Scheme 5). For aldehyde **22a**, protection of the primary alcohol as the benzyl ether and removal of the TBDPS group with nBu$_4$NF yielded alcohol **27a**. Although a host of oxidants were found unsuitable for alcohol **27a** due to epimerization and over-oxidation to the carboxylic acid, the use of TEMPO was found to reliably furnish aldehyde **22a** in 87% yield. [15] Alternatively, J ring alcohol **10** was protected with benzoyl chloride in the presence of DMAP to provide the benzoate ester, which was subjected to nBu$_4$NF as before to deliver alcohol **27b** in 91% over two steps. Once again, TEMPO proved to be the oxidant of choice for formation of the sensitive aldehyde **22b**.

The HWE coupling of the G and J rings was first explored for keto phosphonate **21a** and aldehyde **22a** (Scheme 6). As in the BCDE synthesis, exposure to $Ba(OH)_2$ smoothly furnished enone **28a** in 80% yield. Clean 1,4-reduction with 40 mol% of Stryker's reagent produced the ketone, and the acetonide protecting group was swiftly removed using TFA in refluxing MeOH to afford diol **29a** in 88% yield over two steps. The keto phosphonate **21b** and aldehyde **22b** were coupled and converted to the corresponding diol **29b** following the same three-step protocol, though in slightly diminished yield.

The cyclodehydration of ketodiol **29a** to form the I ring (Scheme 7) was met with considerable resistance, as both the desired enol ether and the starting material were observed to degrade into a complex mixture of intractable products under even moderately acidic conditions, particularly upon heating above 50 °C. Furthermore, conversion of the starting material was often sluggish, indicating the need for rigorous removal of water. It was hoped that the reaction would proceed at room temperature in the presence of strong acid and molecular sieves, but in practice, successful reaction required elevated temperature. Eventually it was found that reaction with PPTS in benzene at 40 °C with azeotropic removal of water under aspirator vacuum (~25 mmHg) smoothly produced the desired endocyclic enol ether in good yield with

minimal decomposition. Protection of the axially disposed C39 hydroxyl as its benzyl ether with KHMDS and BnBr then yielded ether **30**.

The stage was then set for the critical enol ether hydration/oxidation sequence. While selective olefin hydration was achieved in the BCDE system through the use of DMDO/iBu$_2$AlH, the absence of other double bonds in the GHIJ system allowed for hydroboration/oxidation of the I ring enol ether **30**. While BH_3•DMS was unsatisfactory, BH_3•THF allowed for a 91% yield of a 3:1 mixture of separable diastereomers **31** and **32** after alkaline peroxide work-up.[16] The isomers were separately oxidized under Dess–Martin conditions to the corresponding ketones **33** and **34**, respectively. While the minor epimer **34** was isomerized to the major epimer **33** with DBU at 40 °C in good yield, the major epimer **33** could not be isomerized to the minor ketone **34** under identical conditions. The major isomer was therefore reasoned to have the desired configuration at C34, since having the G ring substituent in an equatorial position on the I ring would be more thermodynamically favorable.

To complete the GHIJ fragment, the PMB protecting group of ketone **33** was oxidatively removed with DDQ, and the resulting hemiketal was treated with PPTS in MeOH to form mixed methyl ketal **35**. Reductive etherification mediated by BF_3•Et_2O and Et_3SiH then completed GHIJ tetracycle **20a** in excellent yield as a single isomer. [17]

To our surprise, the cyclodehydration of ketodiol **29b** (Scheme 8) did not proceed well using the previously employed conditions. However, treatment with P_2O_5 in toluene at −30 °C delivered the endocyclic enol ether in good yield. Acylation of the C39 hydroxyl with benzoyl chloride and DMAP in pyridine with heating provided the benzoate-protected enol ether **36**. Similar to before, BH_3•THF was effective (95% yield) for the hydroboration of the enol ether, but in this case, the hydration product obtained after oxidative work-up was an inseparable mixture of diastereomers (dr = 2:1). Other reagents for hydroboration, including 9-BBN and enantiopure (Ipc)BH_2,[18] were probed with the intention of increasing the diastereoselectivity of the reaction, but inferior results were obtained. Thus, the mixture of diastereomers was oxidized to ketone **37** (2:1 mixture of inseparable epimers) under Dess–Martin conditions, and exposure to DBU increased the diastereomeric ratio to 6:1. At this point, it was postulated that removal of one or more hydroxyl protecting groups might allow for separation of the epimers. Though we favored selective removal of the PMB groups with DDQ at this juncture in order to access the targeted tetracycle **20b** (Figure 2), the resulting diols remained an inseparable mixture. On the other hand, hydrogenolysis of both PMB groups and the benzyl group using Pearlman's catalyst lead to triol **38**,[19] from which the minor, undesired isomer 34-*epi*-**38** was easily removed via chromatography. Ketalization with PPTS in MeOH lead to mixed methyl ketal **39**, and reductive etherification under conditions used before accomplished a shortened synthesis of the GHIJ fragment **40** in excellent yield.

Coupling of the BCDE and GHIJ Fragments, and Completion of Brevetoxin A

The planned approach for the completed total synthesis of brevetoxin A focused on an endgame that would exploit the selective manipulation of nonacycle **2** (vide supra, Scheme 1). The nonacycle **2** would derive from a stereoselective Horner–Wittig coupling[20] of phosphine oxide **3** and aldehyde **4**, which found precedent in the strategy previously reported by Nicolaou.[21] We recognized that the dithioketal moiety of aldehyde **4** offered versatility, as it could serve as a stabilized precursor to a mixed ketal (**2**, X = OMe), or lead to a mixed *S*,*O*-ketal (**2**, X = SO_2Et) in the event that formation or reductive etherification of the less activated nonacycle proved problematic.

The next task became the manipulation of the tetracyclic fragments **5** and **20a** or **40** to the required Horner–Wittig coupling partners. To this end, the conversion of diol **5** to phosphine oxide **3** (Scheme 9) commenced with protection of diol **5** as the bis-*p*-methoxybenzyl ether

with subsequent reductive cleavage of the benzyl ethers with LiDBB to form diol **41**. Protection of the diol as the bis-TBS ether and selective cleavage of the primary TBS ether with HF•pyr afforded alcohol **42**. Smooth transformation to phosphine oxide **43** was then accomplished via mesylation of the alcohol, nucleophilic displacement of the mesylate to provide the phosphine, and finally, oxidative workup of the phosphine with H_2O_2.[20,21] Cleavage of the silyl ether **43** with *n*Bu_4NF and formation of the methoxypropyl (MOP) acetal delivered the required phosphine oxide **3** in high yield.[22]

For the GHIJ fragment, tetracycle **20a** was treated with *n*Bu_4NF, and the resultant secondary alcohol was oxidized to the ketone **44** under Dess–Martin conditions (Scheme 10). Reaction of ketone **44** with $Zn(OTf)_2$ and EtSH produced the dithioketal,[23] and reductive cleavage of the pivaloate ester delivered alcohol **45**. While most conditions proved to be unsuitable for the subsequent oxidation of the primary alcohol to dithioketal aldehyde **46** due to undesired oxidation of the dithioketal, the use of stoichiometric *n*Pr_4NRuO_4 cleanly provided the desired aldehyde.[24]

As for the alternative GHIJ tetracycle **40**, the primary hydroxyl was selectively protected as the TBS ether (Scheme 11), and the remaining secondary hydroxyl was oxidized under buffered Dess–Martin conditions to afford ketone **47**. Removal of the silyl protecting group with H_2SiF_6 provided the hydroxy ketone, and exposure to $Zn(OTf)_2$ in 1:1 EtSH:CH_2Cl_2 reliably furnished dithioketal **48**. As before, reaction with one equivalent of *n*Pr_4NRuO_4 delivered aldehyde **49** in good yield.

Having both phosphine oxide **3** and aldehydes **46** and **49** in hand, we then explored their assembly under Horner–Wittig conditions (Scheme 12).[20] After some experimentation, addition of 3 equiv of LDA to a solution of phosphine oxide **3** and aldehyde **46** at −78 °C was found to produce 63% of the Horner–Wittig adduct. It is worthy of note that no epimerization of aldehyde **46** was observed despite the presence of superstoichiometric base.[25] Exposure of the intermediate hydroxy-phosphine oxide to $KN(SiMe_3)_2$ provided the desired *Z*-olefin **50** in 74% yield. In contrast, when phosphine oxide **3** and aldehyde **49** were reacted in the presence of three equivalents of LDA, the desired Wittig adduct was obtained in only 28% yield, along with an additional 14% of adduct in which the primary benzoate ester had been cleaved. Treatment of the Wittig adducts with $KN(SiMe_3)_2$ was also complicated by the loss of benzoate protecting groups and unidentified degradation, producing olefins **51** and **52** in an unacceptable 32% combined yield. Further attempts to identify cleaner elimination conditions by altering the base, solvent, and temperature were unsuccessful.

After carrying out the effective coupling of the BCDE **3** and GHIJ **46** fragments, we focused on mixed methyl ketal **54** as a precursor to the targeted nonacycle **55** (Scheme 12). Despite the rarity of the conversion of 7-hydroxy ketones or ketals to eight-membered cyclic ketals found in the literature, we believed that the formation of mixed ketal **54** should be possible due to the structural pre-organization appearing in olefin **50**. Specifically, we expected the C24–C25 *Z*-olefin, along with the conformational constraints about the C21–C22 and C26–C27 bonds, to facilitate the required cyclization event. In addition, based upon the reported use of $(F_3CCO_2)_2IPh$ in alcoholic solvent to convert dithioketals to dialkoxy ketals,[26] we presumed that treating olefin **50** with the hypervalent iodine reagent in MeOH would lead to the dimethyl ketal **53**, or to mixed ketal **54** directly. In the event, treatment of olefin **50** with $(F_3CCO_2)_2IPh$ in MeOH rapidly removed the MOP protecting group, and led to a mixture of the expected ketal products in a 4:1 ratio favoring the dimethyl ketal **53**.[27] Upon exposure of the crude mixture to PPTS, an 80% overall yield of mixed methyl ketal **54** was obtained.

In view of our previous successes in the reductive etherification of precursors to the BCDE and GHIJ fragments (vide supra, Schemes 3, 7, and 8), it was anticipated that treatment of ketal

54 with an appropriate Lewis acid in the presence of a trialkylsilane would deliver the expected nonacycle **55**. Despite extensive screening of Lewis acids (BF_3•OEt_2, $TiCl_4$, TMSOTf), solvents, and silanes (Et_3SiH, Me_2PhSiH), only traces of the desired product **55** were observed. Instead, hydrolysis of the ketal and intractable decomposition were repeatedly observed.[28] Drying agents (4 Å MS, BaO) were investigated in an effort to suppress hydrolysis, but under these conditions, cleavage of the central oxocene (producing the C27 methyl ether) was the major product. This result indicated that the kinetically preferred mode of C–X bond cleavage for the methyl ketal substrate involved good $n_O \rightarrow \sigma^*_{C27\text{-}O}$ orbital overlap (Figure 3), leading to a ring-opened oxocarbenium ion which is intercepted by silane. We reasoned that the precedented sulfone leaving group[21,29] would circumvent this unwanted stereoelectronic effect, since the absence of lone pair electrons on sulfur would render the $n \rightarrow \sigma^*_{C27\text{-}O}$ interaction impossible. Instead, the required mode of bond cleavage should be favored (Figure 3). The increased lability of the sulfinate leaving group relative to the methoxide nucleofuge was also expected to facilitate the desired reactivity.

Turning our attention to the reductive etherification of sulfone **58** (Scheme 13), the MOP acetal was removed from olefin **50** under acidic conditions, and the resulting hydroxy dithioketal **56** was treated with $AgClO_4$ to provide the mixed *S,O*-ketal **57**. Subsequent oxidation with *m*CPBA led to sulfone **58**, and reductive etherification with concomitant removal of the PMB protecting groups was smoothly accomplished to furnish diol **59** in 85% yield. While the A ring lactone **60** was readily accessible in 83% yield from diol **59** through exposure to PhI $(OAc)_2$ and catalytic TEMPO, [30] clean debenzylation was not observed under a variety of conditions.Nevertheless, brevetoxin A (**1**) was accessed in three steps from diol **59** (Scheme 14). Reductive cleavage of the benzyl ethers with LiDBB[31] delivered tetraol **61**, which was exposed to $PhI(OAc)_2$ and catalytic TEMPO to selectively form the A-ring lactone and the C44 aldehyde while leaving the axially-disposed C39 secondary alcohol untouched.[30] The unpurified decacyclic aldehyde **62** was treated with Eschenmoser's salt in the presence of Et_3N[21,32] to complete the synthesis of brevetoxin A (**1**).[33] Synthetic brevetoxin A (**1**) was identical in all respects (1H and ^{13}C NMR, IR, HRMS, $[\alpha]_D$) to an authentic sample.[21,34]

Conclusion

In summary, the second total synthesis of brevetoxin A has been accomplished in a highly convergent, enantioselective fashion. The synthesis hinges on the selective oxidation of a late-stage nonacyclic tetraol. Access to the key tetraol intermediate was explored via the uncommon cyclization of a medium ring mixed methyl ketal, which was assessed as a substrate for oxocene-forming reductive etherification. In the end, a sulfone-based approach proved to be a superior path to the nonacyclic tetraol. A Horner–Wittig olefination of two advanced tetracyclic subunits assembled the eventual tetraol precursor, with the tetracyclic units being constructed via a common [X + 2 + X] strategy through a Horner–Wadsworth–Emmons coupling and subsequent cyclodehydration/reductive etherification protocol. Each of the monocyclic units for the construction of the tetracyclic BCDE and GHIJ units was prepared from a ring-closing metathesis of an acyclic diene precursor with stereodefined ether linkages. Enolate methodologies developed in our laboratory were exploited to introduce eight of the 22 stereocenters present within brevetoxin A.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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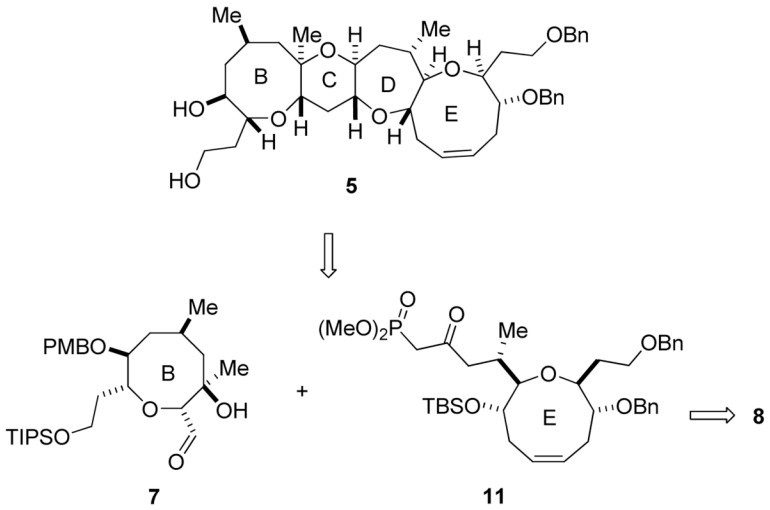


Figure 1.
[X + 2 + X] strategy for the BCDE tetracycle **5**.

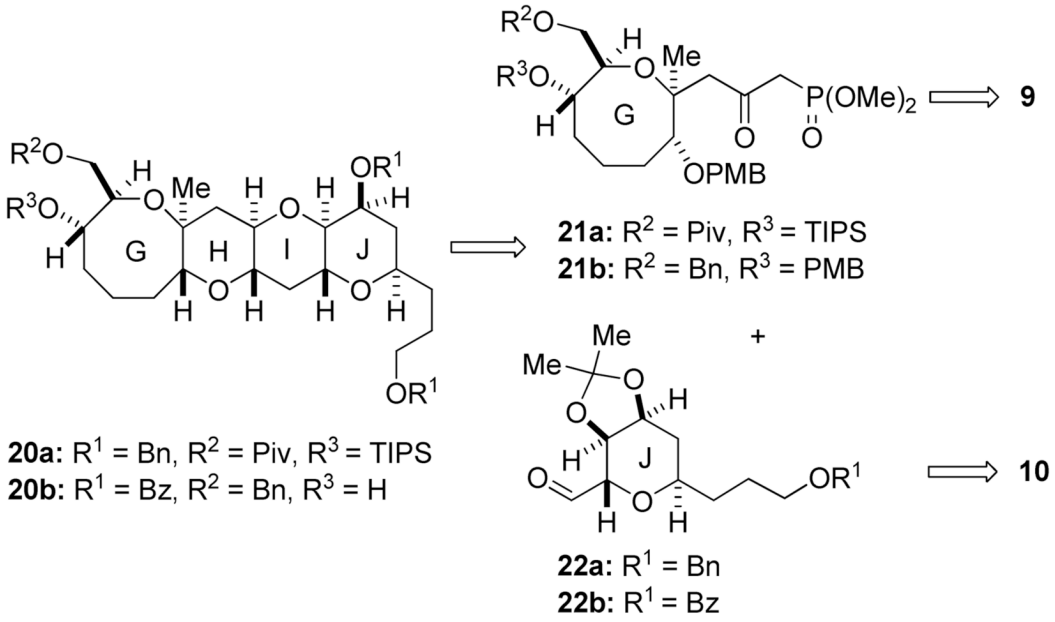


Figure 2.
[X + 2 + X] strategy for the GHIJ fragment.

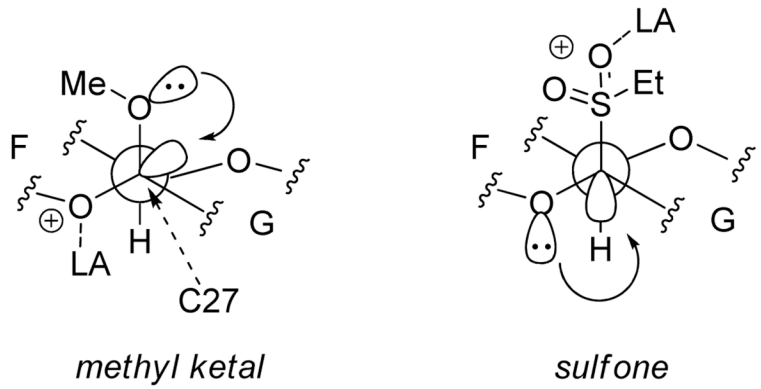
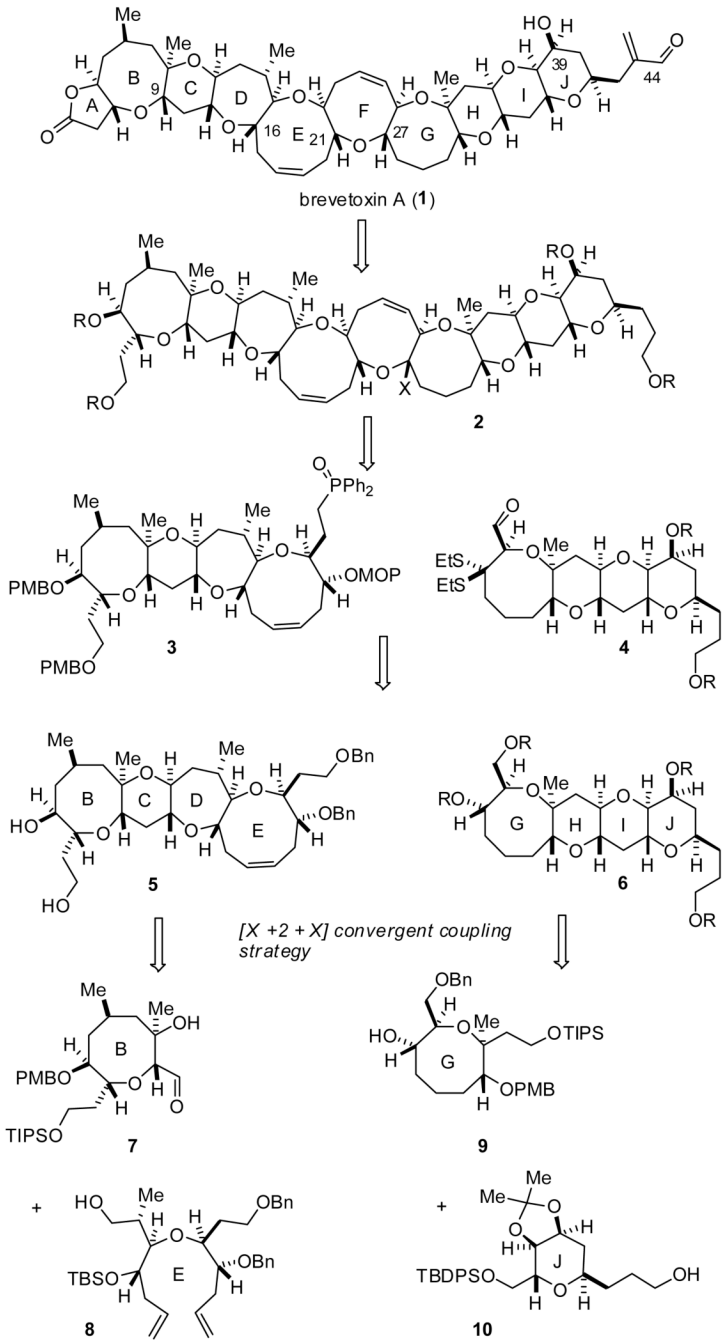
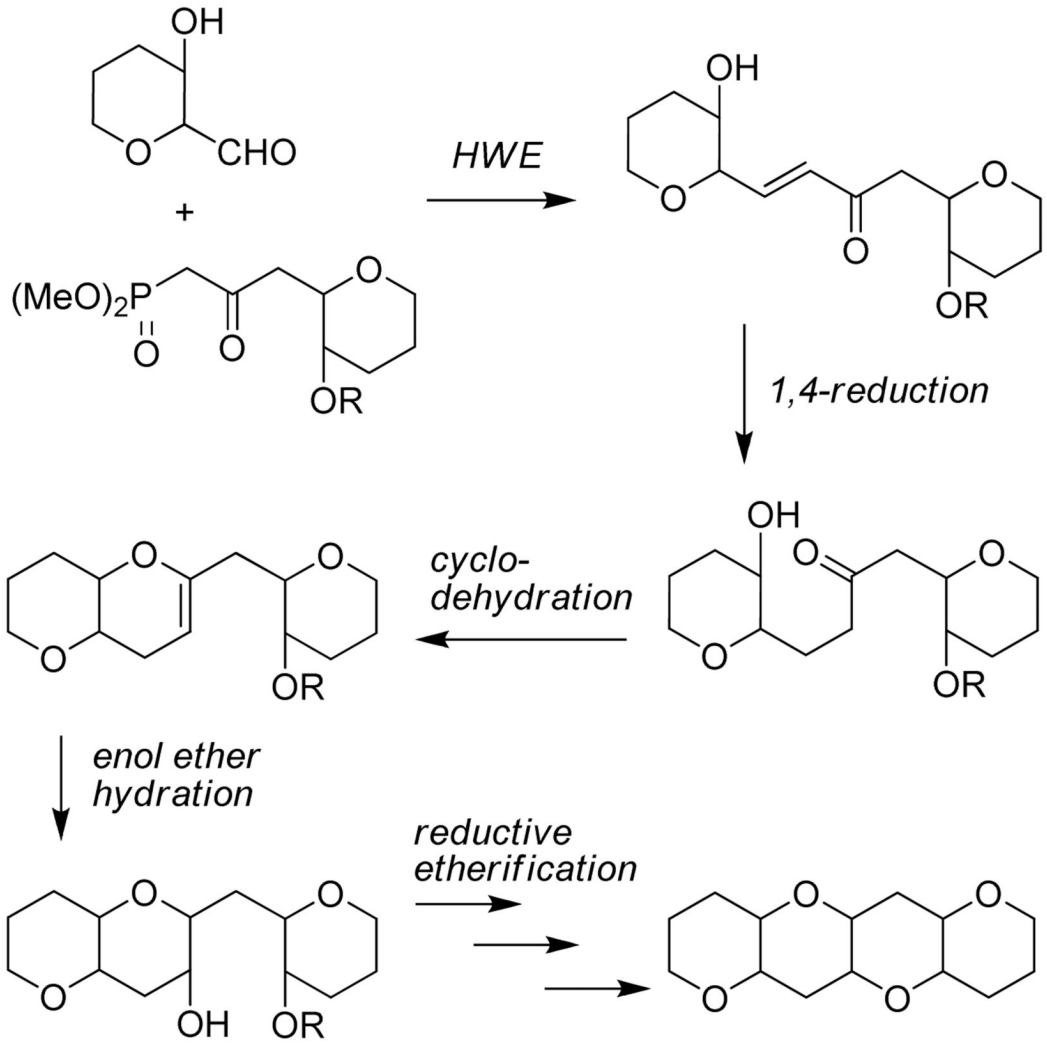


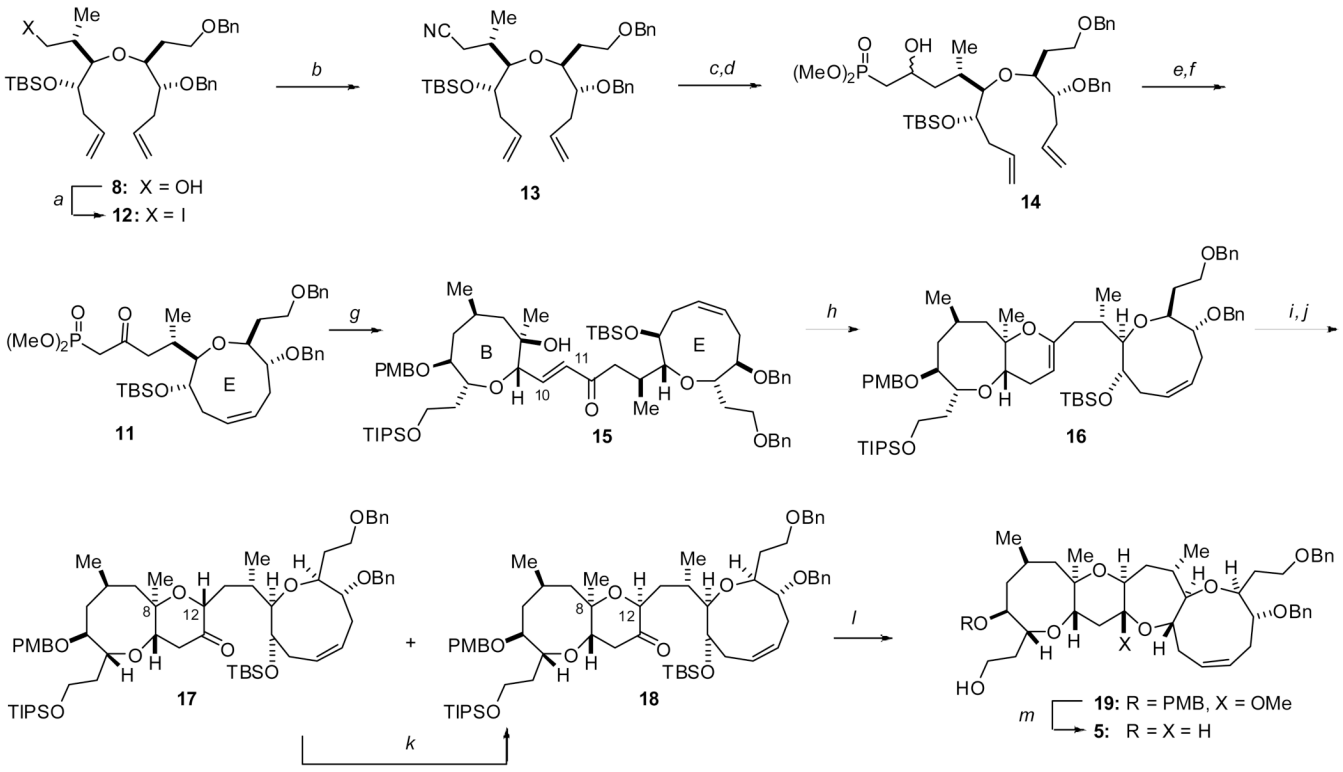
Figure 3.
Favored modes of C-X bond cleavage for methoxy ketal and sulfone substrates.



Scheme 1.
Retrosynthetic analysis of brevetoxin A.

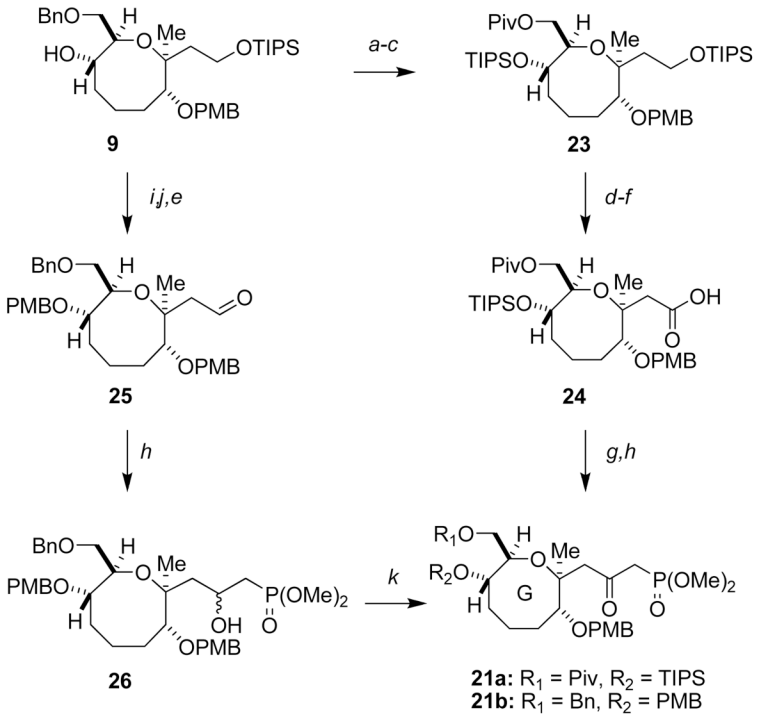


Scheme 2.
Convergent coupling strategy to form tetracyclic polyether arrays.



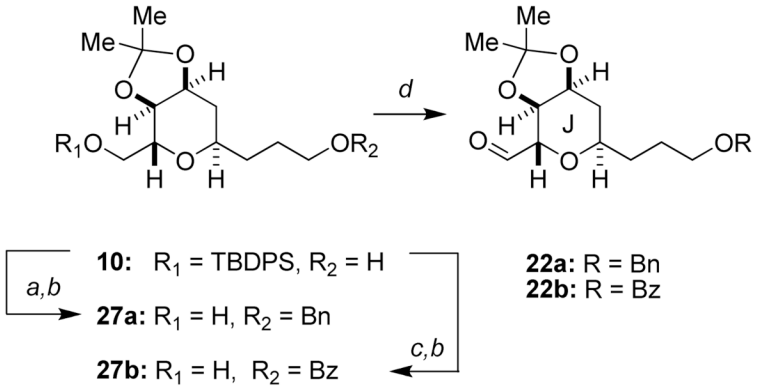
Scheme 3.

Synthesis of the BCDE tetracycle **5**. Reagents and conditions: a) PPh_3, I_2, imid., C_6H_6, 97%; b) NaCN, DMSO, 96%; c) *i*Bu_2AlH, CH_2Cl_2, 0 °C, 84%; d) $(MeO)_2P(O)CH_3$, *n*BuLi, THF, −78 °C, 88%; e) Dess–Martin periodinane, CH_2Cl_2, 96%; f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C, (quant.). g) **7**, $Ba(OH)_2$, THF, H_2O, 96%; h) $(PPh_3)_3RhCl$, Me_2PhSiH, PhMe, 50 °C; PPTS, 92%; i) DMDO, CH_2Cl_2, −78 °C; *i*Bu_2AlH; j) Dess–Martin periodinane, CH_2Cl_2, 67% (3:1 dr) for 2 steps; k) K_2CO_3, MeOH, 65 °C, 66% (84% brsm); l) CSA, MeOH, 65 °C, 76%; m) $BF_3{\bullet}OEt_2$, Me_2PhSiH, CH_2Cl_2, 0 °C, 78%.



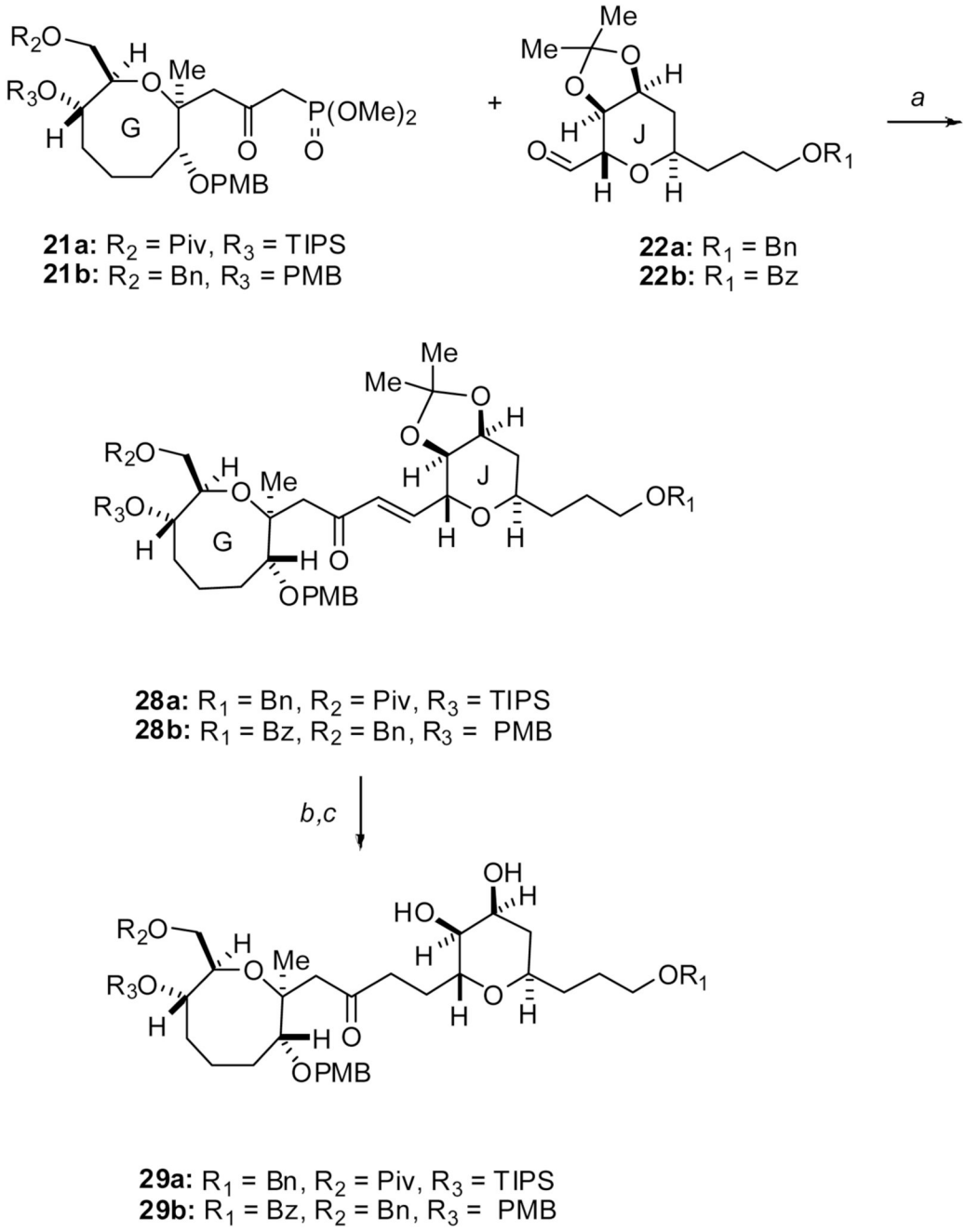
Scheme 4.

Completion of G ring keto phosphonates **21a** and **21b**. Reagents and conditions: a) TIPSOTf, 2,6-lut., CH_2Cl_2, 0 °C; b) LiDBB, THF, −78 °C; c) PivCl, DMAP, Et_3N, CH_2Cl_2, 90% (3 steps); d) TFA, THF, H_2O, 96%; e) TEMPO, NaOCl, KBr, CH_2Cl_2, H_2O, 0 °C, 97%; f) $NaClO_2$, $Me_2C{=}CHMe$, *t*BuOH, pH 4 buffer, 98%; g) K_2CO_3, MeI, DMF, 96%; h) $LiCH_2(O)P(OMe)_2$, THF, −78 °C, 87% (for **21a**), 89% (for **26**); i) NaH, PMBBr, $nBu_4N^+I^-$, THF, 0 °C to RT; j) H_2SiF_6, CH_3CN, 89% (2 steps); k) Dess–Martin periodinane, CH_2Cl_2, 92%.



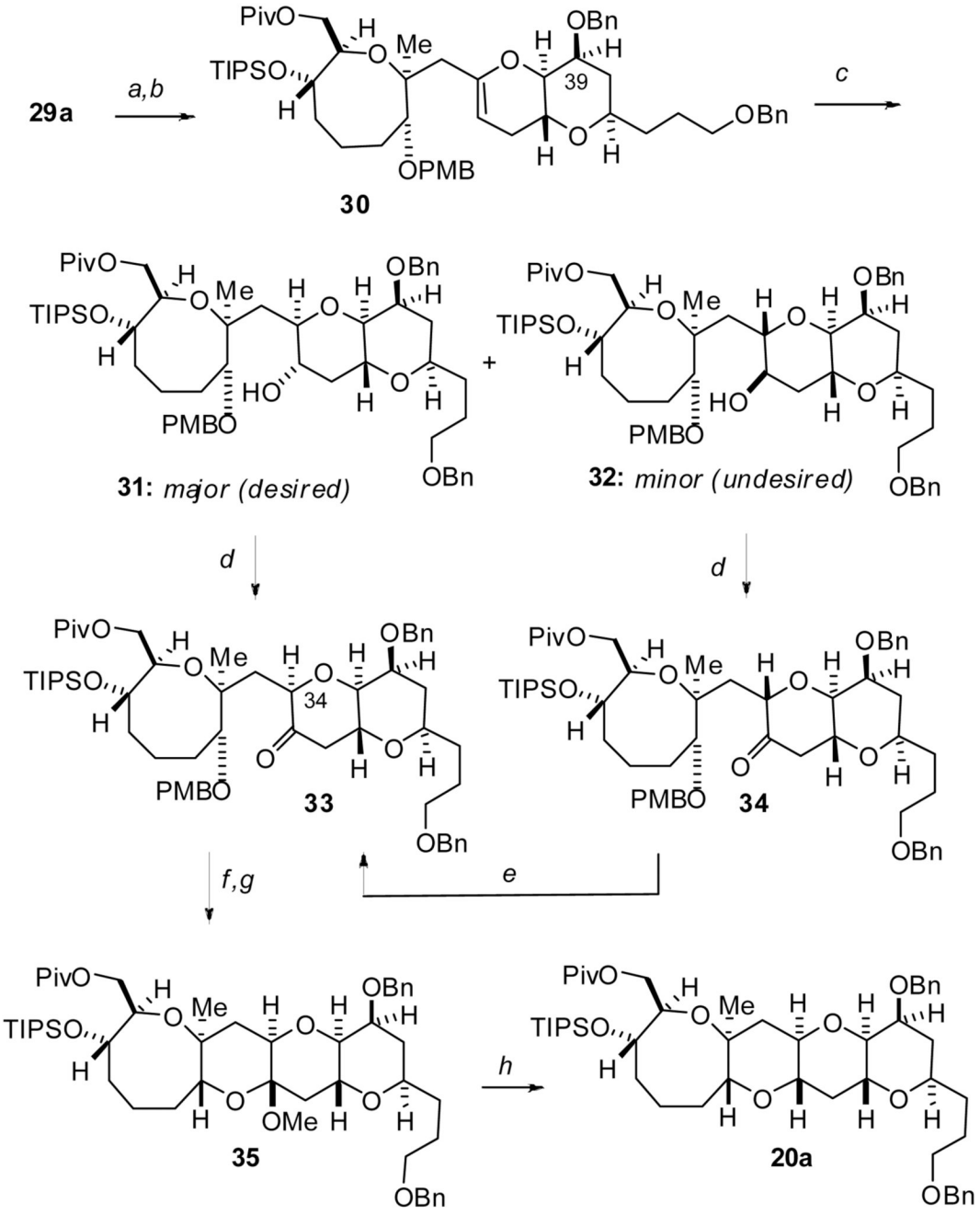
Scheme 5.

Completion of J ring aldehydes **22a** and **22b**. Reagents and conditions: a) KH, BnBr, nBu$_4$N$^+$I$^-$, THF, 0 °C, 88%; b) nBu$_4$NF, THF, 99% (for **27a**), 100% (for **27b**); c) BzCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C, 91%; d) TEMPO, NaOCl, KBr, CH$_2$Cl$_2$, H$_2$O, 0 °C, 87% (for **22a**), 70% (for **22b**).



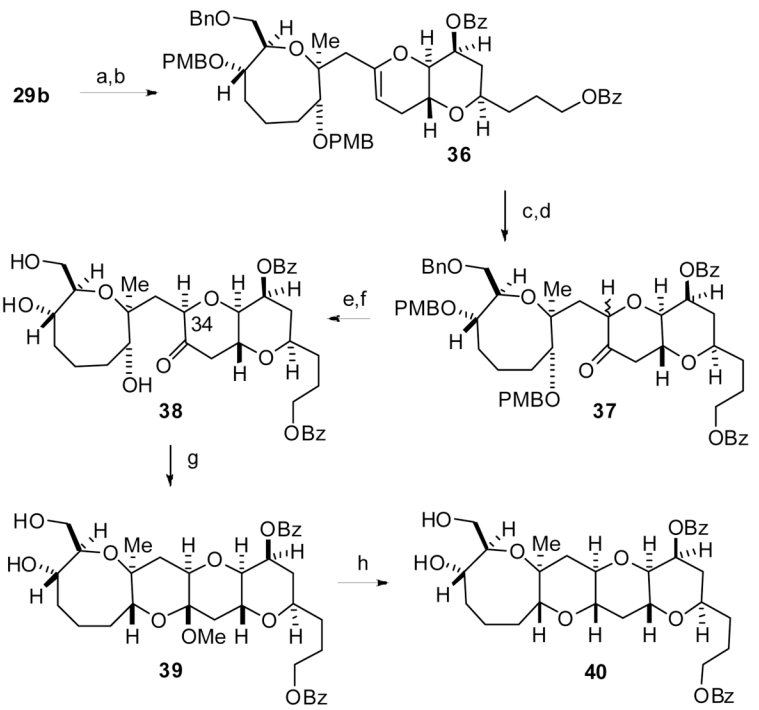
Scheme 6.

HWE coupling of the G and J rings. Reagents and conditions: a) $Ba(OH)_2$, H_2O, THF, 80%; b) $[Ph_3PCuH]_6$ (40 mol%), PhMe, 95% (from **28a**), 89% (from **28b**); c) TFA, MeOH, 65 °C, 93% (for **29a**), 83% (for **29b**).



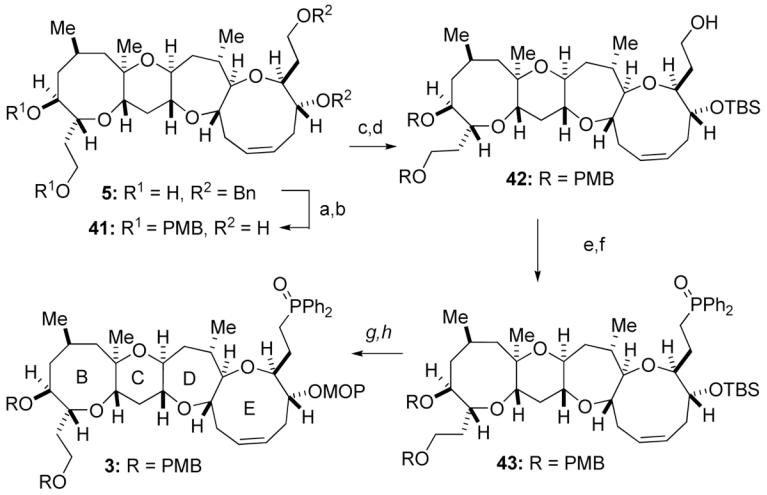
Scheme 7.

Completion of GHIJ fragment **20a**. Reagents and conditions: a) PPTS, C_6H_6, 40 °C, 50 mm Hg, 82% brsm; b) $KN(SiMe_3)_2$, BnBr, $Bu_4N^+I^-$, THF, 0 °C to RT, 92%; c) BH_3•THF, THF, 0 °C, 91% (dr = 3:1); d) Dess–Martin periodinane, CH_2Cl_2, 96% (from **31**), 80% (from **32**); e) DBU, CH_2Cl_2, 40 °C, 85% brsm; f) DDQ, CH_2Cl_2, pH 7 buffer, 89%; g) PPTS, MeOH, 65 °C, 87%; h) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, −30 to 0 °C, 96%.



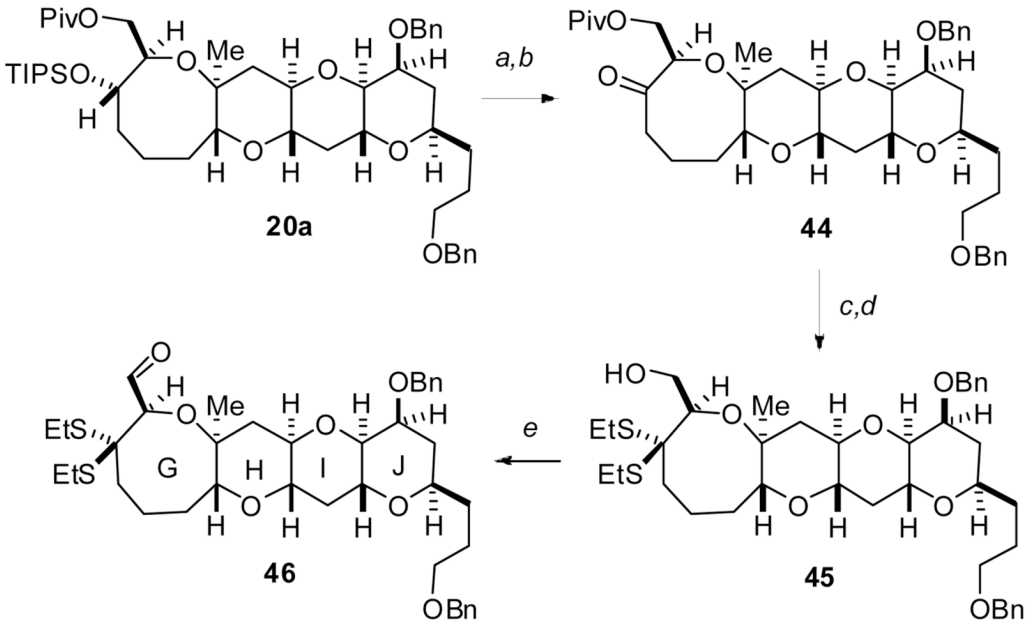
Scheme 8.

Completion of alternative GHIJ fragment **40**. Reagents and conditions: (a) P_2O_5, PhMe, −30 °C, 80% (95% brsm); (b) BzCl, DMAP, pyr., 60 °C, 95%; (c) BH_3•THF, THF, 0 °C; (d) Dess–Martin periodinane, CH_2Cl_2, 87% (2 steps), dr = 2:1; (e) DBU, CH_2Cl_2, 40 °C; (f) H_2, Pd $(OH)_2$, THF, 68% (2 steps); (g) PPTS, MeOH, 65 °C, 80%; (h) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, −30 to 0 °C, 95%.



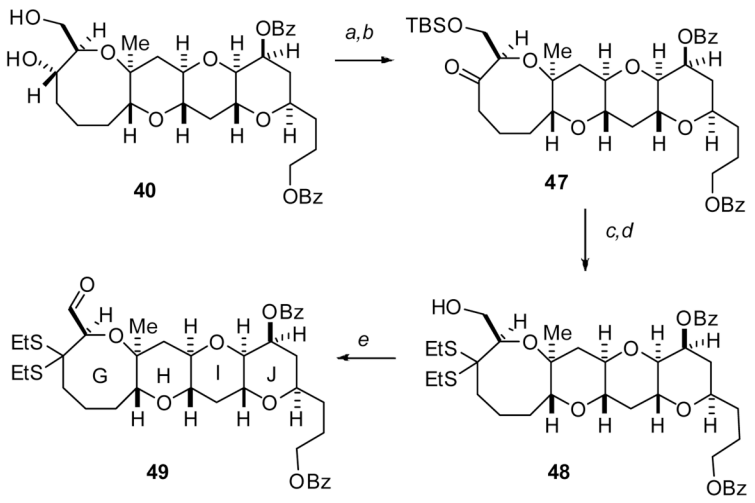
Scheme 9.

Formation of phosphine oxide **3**. Reagents and conditions: a) NaH, PMBBr, DMF, 91%; b) LiDBB, THF, −78 °C, 89%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; d) HF·pyr, THF, 86%; e) MsCl, Et_3N, 0 °C; f) *n*BuLi, $HPPh_2$, THF, 0 °C; H_2O_2, 94%; g) *n*Bu_4NF, THF, 94%; h) 2-methoxypropene, PPTS, 0 °C, 90%.



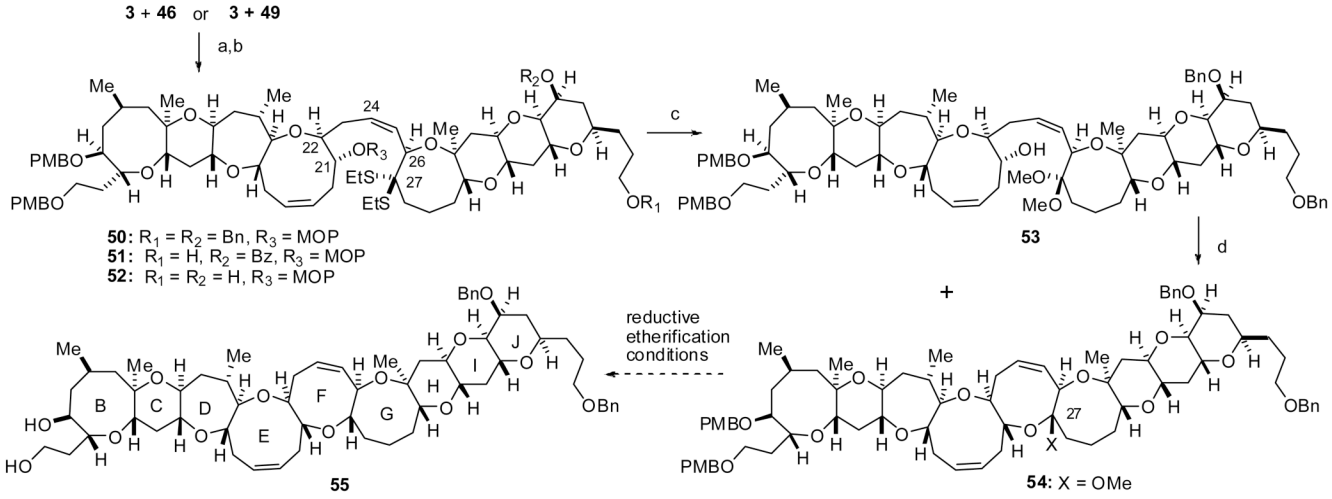
Scheme 10.

Preparation of aldehyde **46**. Reagents and conditions: a) nBu$_4$NF, THF, 0 °C, 94%; b) Dess–Martin periodinane, CH_2Cl_2, 95%; c) Zn(OTf)$_2$, EtSH, CH_2Cl_2, 97%; d) $LiAlH_4$, Et_2O, 0 °C, 85%; e) nPr$_4$NRuO$_4$, 4 Å MS, CH_2Cl_2, 75%.



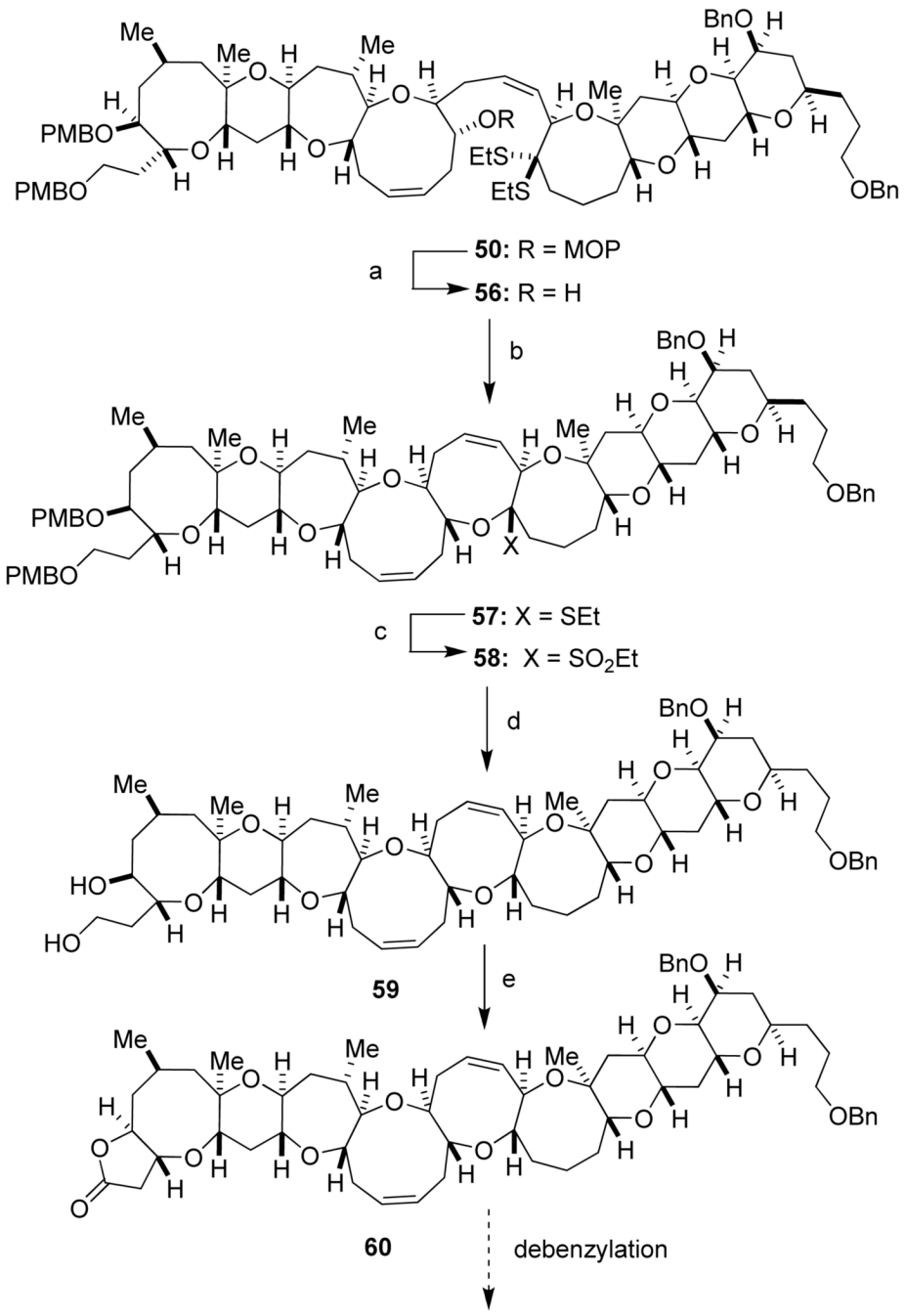
Scheme 11.

Preparation of aldehyde **49**. Reagents and conditions: a) TBSCl, imid. CH_2Cl_2, 94%; b) Dess–Martin periodinane, pyr., CH_2Cl_2, 87%; c) H_2SiF_6, CH_3CN, H_2O, 97%; d) $Zn(OTf)_2$, EtSH, CH_2Cl_2, 87%; e) nPr$_4$NRuO$_4$, 4 Å MS, CH_2Cl_2, 75%.



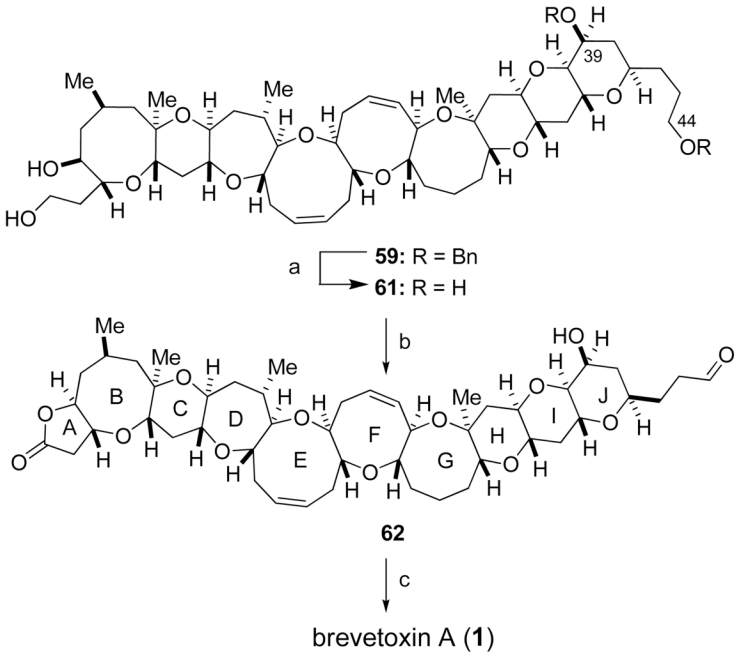
Scheme 12.

Coupling of tetracyclic fragments **3** and **46**. Reagents and conditions: a) LDA, THF, −78 °C, 63% (from **3** + **46**), 42% (from **3** + **49**); b) $KN(SiMe_3)_2$, DMF, 74% (for **50**), 32% (for **51** and **52**, combined yield); c) $(F_3CCO_2)_2IPh$, MeOH; d) PPTS, $CH(OMe)_3$, PhMe, 50 °C, 80% for 2 steps.



Scheme 13.

Closure of the A and F rings. Reagents and conditions: a) PPTS, MeOH, 0 °C, 96%; b) $AgClO_4$, $NaHCO_3$, 4 Å MS, $MeNO_2$, 65%; c) *m*CPBA, CH_2Cl_2, 0 °C, 74%; d) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, −78 to 0 °C, 85%; (e) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 83%.



Scheme 14.

Completion of brevetoxin A. Reagents and conditions: a) LiDBB, THF, −78 °C, 86%; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2; d) $H_2C{=}NMe_2{}^+I^-$, Et_3N, CH_2Cl_2, 48% for 2 steps.